REMARKS

Section 103 Rejections

Claims 1-3 and 5-11 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over Qian et al., Effreth et al., Zheng et al., Venugopalan et al, and Li et al., and further in view of Crooks et al. Claims 8, 9 and 11 have been canceled. Claim 10 has been amended to be dependent on claim 5. This ground of rejection is respectfully traversed.

The Qian et al. reference mentions the antiviral activity of artemisinin against influenza type A_3 virus. This is a very different type of virus than the *Flaviviridae* sp. of the present claims. The taxonomy of viruses[1] classifies Influenza A to Group V: (-) sense RNA viruses of the family Orthomyxoviridae, whereas *Flaviviridae* sp. are classified to Group IV: (+) sense RNA viruses of the family Flaviviviridae. Those skilled in the art recognize that viruses of different groups and families respond very differently to antivirals. There is no predictability that antiviral effects seen in one group or family of viruses will be exhibited in a different group of family of viruses. Any teaching of the activity of artemisinin against Influenza A viruses does not make obvious the activity of artemisinin or any of the other compounds of claim 1 against *Flaviviridae* sp. Indeed, the next reference cited by the Examiner reinforces this point. The Efferth et al. reference discloses that artesunate did not show antiviral activity against Influenza A viruses. Thus, we have one article that shows activity of artemisinin against Influenza A viruses and another that shows no activity of the related compound artesunate against the same viruses.

Efferth et al. does, however, teach activity of artesunate against HCMV and HSV-1, both of which belong to Group I: ds DNA viruses of the family Herpesviridae. Again, any teaching of the activity of artesunate against HCMV and HSV-1 viruses does not make obvious the activity of artesunate or any of the other compounds of claim 1 against *Flaviviridae* sp.

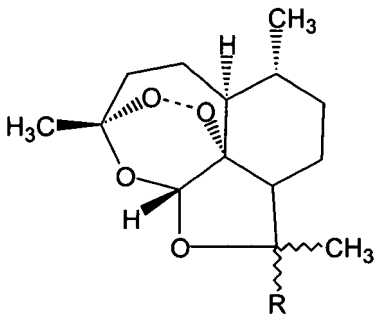
Zhang et al. describe the effect of artemether against epidemic hemorrhagic fever virus. This virus belongs to Group V: (-) sense RNA viruses of the family Bunyviridae. Again, any teaching of the activity of artemether against epidemic hemorrhagic fever virus does not make obvious the activity of artemether or any of the other compounds of claim 1 against *Flaviviridae* sp.

---

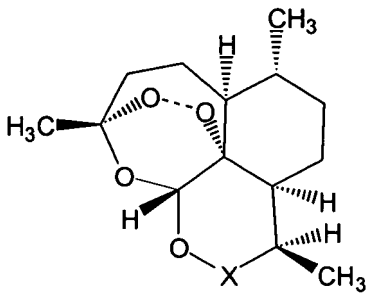
[1] H.V. Van Regenmortel, D. Bishop, M. Van Regenmortel, C. Fauquet (Eds). Virus taxonomy:eighth report of the international committee on taxonomy of viruses. Academic Press (2005).

Li et al. teach nothing with respect to the antiviral activity of any compounds. Li et al. state merely that their compounds "...were prepared as antitumor, antiviral and antiparasitic compounds. No proof whatsoever of the antitumor, antiviral or antiparasitic activities of any compounds was provided. Li et al. teaches nothing to those skilled in the art about antiviral activity of any compounds.

Venugopalan et al. describe the activity of a specific class of compounds against Friend's leukemia virus. This virus belongs to Group VI: RNA reverse transcribing viruses of the family Retroviridae. The compounds of Venugopalan et al. are distinct from the compounds of the present invention, as shown below:



Venugopalan molecules



Kemin molecules

Again, any teaching of the activity of the distinct molecules of Venugopala et al. against Friend's leukemia virus does not make obvious the activity of any of the compounds of claim 1 against *Flaviviridae* sp.

All the antiviral activities mentioned above of artemisinin or its derivatives, were against viruses belonging to a different virus Family, even belonging to a different virus Group than the Flaviviridae claimed in the present applicatioin. Moreover, the present application itself establishes that artemisinin does not possess a broad antiviral spectrum. Reproduced below is Table 1 of the present application:

Table 1 - Results of screenings against HIV-1, HIV-2, HSV-1, HSV-2, VV, CMV and VZV

Compound	[a]EC50 (μg/ml)								
	HIV-1 (III_B) (CEM)	HIV-2 (ROD) (CEM)	HSV-1 (KOS) (E_6SM)	HSV-2 (G) (E_6SM)	VV (E_6SM)	CMV Davis (HEL)	CMV AD-169 (HEL)	VZV (HEL)	VZV (HEL)
								OKA	YS
Artemisinin	> 20	>20	> 400	240	240	> 50	> 50	> 50	> 50
KE-4	> 20	>20	> 80	> 80	> 80	> 50	> 50	> 50	> 50
KE-5	> 100	> 100	> 240	> 80	> 80	> 50	> 50	> 50	> 50
KE-6	> 20	> 20	> 80	> 80	> 80	10	33	17	30

There is no prior art regarding the activity against Flaviviridae. Known antiviral products are, if active against multiple viruses, often only active against viruses of the same virus Group. Additionally, following the publications of the results disclosed in the present application, other articles have been published in peer review scientific journals that report on the activity of artemisinin against Flaviviridae, indicating that the scientific community considers this as a valuable, novel scientific finding.[2] These articles are evidence in support of nonobviousness under Graham v. John Deere Co., 383 U.S. 1 (1966),

The Examiner cites Crooks et al. for the proposition that a compound that augments cell-mediated immunity is useful for the treatment of tumors and viral infections, such as hepatitis C infection in a replicon model. However, the compounds of the present invention show a concentration dependant effect in a hepatitis C replicon model, establishing that the compounds of claim 1 possess antiviral activity *per se* and are not dependent on any effect on cell-mediated immunity to exert their activity. Hepatitis C replicon replication is not inhibited by IFN-γ in HuH 6 cells. Artemisinin itself resulted in a concentration-dependant decrease in hepatitis C RNA levels in HuH cells without being cytostatic.[3] This points at a different mode of action compared to interferon. Thus, Crooks et al. is not applicable to the present application.

[2] M.R. Romero et al. Antiviral effect of artemisinin from Artemisia annua against a model member of the Flaviviridae family, the Bovine Viral Diarrhoea Virus (BVDV). *Planta Med* 72 (2006) 1169-1174

Accordingly, the purpose of the claimed invention is not taught nor suggested by the cited references, nor is there any suggestion or teaching which would lead one skilled in the relevant art to combine the references in a manner which would meet the purpose of the claimed invention. Because the cited references, whether considered alone, or in combination with one another, do not teach nor suggest the purpose of the claimed invention, Applicant respectfully submits that the claimed invention, as amended, patentably distinguishes over the prior art, including the art cited merely of record.

Based on the foregoing, Applicant respectfully submits that its claims 1-3, 5-7, and 10, as amended, are in condition for allowance at this time, patentably distinguishing over the cited prior art. Accordingly, reconsideration of the application and passage to allowance are respectfully solicited.

The Examiner is respectfully urged to call the undersigned attorney at (515) 288-2500 to discuss any remaining issues that may exist or arise.

Respectfully submitted,

Date: 11 September 2007

Kent A. Herink
Registration No. 31,025
DAVIS, BROWN, KOEHN,
SHORS & ROBERTS, P.C.
666 Walnut St., Suite 2500
Des Moines, Iowa 50309
Telephone: (515) 288-2500

ATTORNEYS FOR APPLICANT

[3] J. Paeshuyse *et al.* Hemin potentiates the anti-hepatitis C virus activity of the antimalarial drug artemisinin. *Biochem Biophys Res Comm* 348 (2006) 139-144